

APIXABAN TOXICITY



“Man Controller of the Universe”, Mural Fresco, 1934, Diego Rivera, Palacio de Belles Artes, Mexico City.

*“It’s not good taste in a man like me”,
Said John D’s Grandson, Nelson.
“To question an artist’s integrity
“Or mention a practical thing like a fee,
“But I know what I like to a large degree.
“Though art I hate to hamper;
“For twenty one thousand conservative bucks
“You painted a radical. I say shucks,
“I never could rent the offices -
“The capitalistic offices,
“For this, as you know, is a public hall
“And people want doves or a tree in fall,
“And although your art I dislike to hamper,
“I owe a **little** to God and Grandper,
“And after all,
“It **my** wall....”*

“We’ll see if it is!”, said Rivera

*E.B White, “I Paint What I See”,
The New Yorker, May 1933.*

Senora Diego Rivera, the comely young wife of the artist whose fresco has been ordered covered - perhaps permanently because of its Communistic viewpoint, is grieved but not perturbed....

A girlish Spanish type, olive skinned, doe-eyed, lithe and slender, she sat down on the edge of her bed in a room filled with friends and sympathizers, and associates of her husband, closed her ears to their excited conversations and told just how she feels about it....

She believes that the Rockefellers have acted so "because they were afraid of public opinion", and she feels very certain that, "Mrs Rockefeller probably feels badly about it". They saw the preliminary sketches with Lenin's portrait, more prominent there than in the painting, she said, and they approved.

"The Rockefellers know quite well the murals were to depict the revolutionary point of view - that they were going to be revolutionary paintings", she said quietly. "They seemed very nice and understanding about it and always very interested, especially Mrs Rockefeller. We were their guests at dinner two or three times, and we discussed the revolutionary movement at great length. Mrs Rockefeller was very nice to us always. She was lovely. She seemed very interested in radical ideas - asked us many questions. You know she helped Mr Rivera at the Museum of Modern Art and really battled for him".

Geraldine Sartain, New York World Telegram, 10 June, 1933

Art has long be used as a means of political propaganda, in particular when a message had to be disseminated to an illiterate population, or in the case of a literate one when a visual image could hold far more power than the written word. The Eighteenth Dynasty Egyptian Pharaoh, Akhenaten, everywhere had images of Aten his new Sun god carved into the walls and temples of public places. During the Seventeenth century, Baroque art was the heavy artillery of the Counter Reformation's battle for souls. Supremacist and Constructivist Art was used to destroy the old Imperial Tsarist order in Soviet Russia in the Twentieth century, later to be replaced by an even harder hitting Socialist (as opposed to Social) Realism.

In the battle for hearts and minds Artists of extraordinary genius were needed. During the Counter-Reformation, the violent and unpredictable Michelangelo Merisi da Caravaggio was the man of the hour. During the century of the great Communist experiment, the man of the hour was the Mexican Artist, Diego Rivera. In the 1930s he was the most famous Artist in the world, and one of the most influential, he carried the message of the Socialist Revolution, not only to his native country, but to the Communist masses the world over.

Rivera was the best known of a group of Socialist Mexican Artists, that included José Clemente Orozco and David Alfaro Siqueiros who were born of the Mexican Revolution and Civil War of 1910 to 1920, that swept away the old aristocratic European ruling class. To spread the revolution to the illiterate masses they brought into being a whole new genre of Art, that came to be known as Mexican Muralism. In 1922 Jose

Vasconcelos the minister for education, began to commission the Muralists to produce large paintings and frescos on grand public buildings. Many of these works were truly monumental in scale, scope and complexity. Although Muralism borrowed aspects of many European genres such as the Renaissance, Symbolism, Expressionism, Post Impressionism and even Surrealism, it combined them with unique aspects of Russian Socialist Realism, Mexican Folk Art, traditional Christian and pre-Columbian motifs. The most radical of the Muralists, David Siqueiros, went so far as to call for a ban of all easel painting; "We condemn so-called easel painting", he declared, "and all the art produced by ultra-intellectual circles on the grounds that it is aristocratic and we glorify the expression of monumental art because it is public property!". With such a radical manifesto, it seemed somewhat incongruous therefore that the highest levels of American capitalism began to commission the Muralists, and Rivera in particular, major works for American companies, most notably Edsel Ford in Detroit, and then the Rockefellers in New York, and all this at the height of the Great Depression.

Although a dedicated Communist, he was in fact the General Secretary of the Mexican Communist Party, Diego was not averse to accepting lucrative commissions from wealthy industrialists, for which he would suffer increasing criticism from his Socialist comrades. By 1930 however the favoured situation of the Muralists had begun to decline. There was no longer unlimited government funding, and the new President Plutarco Calles, was far more conservative than his predecessors. He began to suppress the Communists. These facts, together with Diego's Trotskyist leanings which brought him into conflict with Mexican Stalinists, made the decision to leave Mexico an easy one when he began to receive lucrative commissions from the captains of industry of America. Diego in fact, had great admiration for American Industry, and he envisioned a new "pan- American" culture that would combine the might of northern American know-how with the socialist values of southern America. At the beginning of the Depression, Diego believed that America was ripe for Socialist revolution. His motives for accepting capitalist money were not altogether selfish; he believed he could play a vital role in promoting American Socialism. In turn many powerful American industrialists were fascinated by the Renaissance that was being played out in Mexican Art and they wanted to share in the adventure.

Things went well for Diego and his wife Frida Kahlo in San Francisco, with several commissions, but in 1932 in Detroit, where he produced works for the Ford Motor Company, criticisms began to emerge. His works were a little too Communist for comfort. Although Edsel Ford was tolerant, even supportive, in New York, where his next commission was to be, Diego would find the Rockefellers not quite so open minded.

Caught up in the fame and glamour of the Muralists, the thought that Diego, an avowed Communist, may not be the best person to paint a mural at one of the great capitalist monuments in Manhattan, the Rockefeller Center, never seems to have occurred to its young executive vice-President Nelson Rockefeller. He had himself set the grand theme for the Mural; "Man at the Crossroads, Looking with Hope and High Vision in the Choosing of a New and Better Future". His representatives had approved the preliminary sketches. Nelson had been a supporter of the Ford murals. However by April when the work was two thirds finished, press reports began to appear that were increasingly critical. The New York World Telegram ran with the headline, "Rivera

Paints Scenes of Communist Activity and John D. Jr. Foots the Bill !” Diego had transformed the sketch of a “labour leader” into the unmistakable visage of Lenin. This was simply too much for John D. Rockefeller, Nelson’s father. Either Diego painted out Lenin’s face or the work would come to a halt. Diego feeling his Artistic principles threatened, let alone his Communist ones, refused to comply. On the 9th of May the Rockefeller site manager, accompanied by an army of security staff stormed up to the scaffolding where Rivera was painting and ordered him to cease work. The manager handed him a check for the full balance of the work, then asked Diego to vacate the premises. Diego was thunderstruck and outraged, but there was little he could do about it. Diego’s assistants rushed to the site when they heard what was happening to protest but John D’s mind was made up. Mounted police were called in to clear out the protestors. Nine months later after the Riveras had left New York, the unfinished mural was destroyed.

Neither the Rockefeller family nor Diego would compromise their principles and so the world lost a great work of Art, and so neither were the “winner” out of the whole sorry affair. Diego lost one his major works, the Rockefellers lost their money, though with their vast wealth this hardly mattered at all. Diego did manage a parting shot however. In 1934 back in Mexico City, he received a commission from the government for a mural in the Palace of Fine Arts. Using only a few black and white photographs of the original incomplete New York mural, “Man at the Crossroads”, Diego created a very similar work, “Man, Controller of the Universe” in which he competed his vision of pan - Americanism. We see the progressive forces of science and technology being driven by a central blue eyed American figure who appears to be at the controls of some giant radiating propellers - the engine of industry. These forces can be used for the immeasurable betterment of society. On the right hand side we see a utopian egalitarian society. There is also a warning however. Technology and industry if used for greed and domination can bring oppression and war. On the right hand side appears his revered Lenin, but now also with images of his equally revered Trotsky, Engels and Marx. But mirror imaged to the left of the “controller” we see an image of John D. Rockefeller, sipping martinis with a high-class whore, and indifferent to the suffering of the exploited; a sobering image of the capitalist system. It was an old trick. Michelangelo would immortalize his enemies by depicting their faces in among the souls of the damned. Diego had had his revenge over the Rockefellers.

When we prescribe anticoagulants to our patients we enter into an important contract. The situation needs to be perfectly clear. We must to explain to our patients that while these agents may fulfill their commission by the prevention of ischemic stroke, they also have, like a great Artist, one great and singular purpose, from which they may never be distracted. This is to anticoagulate the blood, and to this end patients must have a clear understanding that this may on occasions entail unwanted consequences. These consequences may come in the form of dangerous bleeding.

APIXABAN TOXICITY

Introduction

Apixaban is a drug from a novel class of non-coumarin anticoagulants, (loosely known as **NOACs** or “**New Oral Anticoagulants**”) which is an orally active **direct Factor Xa inhibitor**.

It offers some significant therapeutic advantages over warfarin, but is more problematic with respect to its haemorrhagic complications.

Most NOAC related bleeding occurs in the context of therapeutic administration, often as a result of drug interactions, renal failure or significant underlying pathology predisposing to bleeding complications.

Clinical experience with deliberate self-poisoning with NOACs is limited.

Assessment and management is further complicated by the poor correlation of anticoagulant activity with classic coagulation tests and the lack of reliable strategies to reverse anticoagulation.

Unlike dabigatran, apixaban does not currently have a specific reversal agent, although work continues on the “decoy” agent **Andexanet Alfa**.

See also separate document on:

- **Apixaban (in Drugs folder)**
- **Andexanet Alfa (in Drugs folder)**

Preparations

Apixaban as:

Tablets:

- 2.5 mg, 5 mg.

Toxicology

Apixaban is an orally active **direct Factor Xa inhibitor**.

This action is in contrast to **warfarin**, which inhibits normal vitamin K metabolism, which is a co-factor that is required for the synthesis of the vitamin K dependent coagulation factors, II, VII, IX and X, (as well as proteins C and S).

It is also in contrast to the heparins which are direct Antithrombin III *activators*, (which inhibit thrombin).

Pharmacology

Advantages compared to warfarin:

- Fast onset of action:

Onset of action is rapid, (within 2 hours) thereby potentially negating the need for initial treatment with a rapidly acting injectable anticoagulant.
- Fast offset of action:

Anticoagulant effect lasts around 12 hours, which is much shorter than warfarin, (48-72 hours). This means toxic effects, if they occur, will not be as long lasting.
- Predictable response:

Anticoagulation response is sufficiently predictable that routine coagulation monitoring is not required - therefore avoids the need for repeated blood tests to monitor activity, and adjust dosages that warfarin therapy requires.

Disadvantages compared to warfarin:

- The routine coagulation monitoring tests (APTT / PT / INR) are *not* indicative of the anticoagulant effect of Apixaban
- There is no current specific antidote for drug reversal, (unlike warfarin which has vitamin K and Prothrombin X as its antidotes or heparin which has protamine as its antidote) which makes management of life threatening bleeding problematic.

Apixaban is an orally active **direct Factor Xa inhibitor** and not a clotting factor depleting agent, as is the case with warfarin. As such the administration of blood clotting products will not be wholly effective in reversing its effects.

Pharmacokinetics

Absorption:

- Apixaban is given orally.
- Bioavailability is around 50 %.
- Peak concentrations are reached 3-4 hours following ingestion.

Distribution:

- Plasma protein binding is around 90%.

- The volume of distribution is moderate at about 21 liters.

Metabolism and excretion:

Elimination is by both hepatic metabolism and renal excretion.

About 30 % is eliminated by renal excretion.

Risk assessment

The NOACs as a group are potent anticoagulant agents and overdose with any amount could result in clinically significant bleeding.

Classic coagulation tests correlate **poorly** with the anticoagulant effect of these agents and have a *limited* role in refining the risk assessment.

There are no published reports of NOAC overdose in children but accidental ingestion of just 1 or 2 tablets will produce significant anticoagulation and an undefined risk of bleeding.

Specific risk factors for adverse events with apixaban include:

- Age older than 75 years
- Low body weight (less than 50kg)
- Moderate or severe renal impairment (Creatinine Clearance < 50mL/min).

Clinical assessment

Overdose of the NOACs does not cause clinical manifestations in themselves, unless complicated by bleeding episodes.

In the absence of co-ingestants, the presence of altered mental status or seizures should be considered to be due to intracranial bleeding until proven otherwise.

Important points of history:

1. Note the dose of the last apixaban tablet
2. Note the time of the last apixaban tablet.
3. Note the indication for treatment with apixaban

Classification of bleeding severity:

Bleeding complications may be classified (somewhat arbitrarily) as:

Mild:

- Local soft tissue hematomas
- Bleeding from minor wounds to non-life threatening regions.
- Bruising
- Gingival bleeding
- Epistaxis
- Haematuria.

Moderate to severe:

- Reduction in Hb of 20gm/L
- Transfusion of 2 units of RBCs
- Bleeding into critical regions:

These may include:

- ♥ Intraocular
- ♥ Intracranial
- ♥ Intrapulmonary
- ♥ Pericardial space
- ♥ GIT
- ♥ Retroperitoneum
- ♥ Peri or Intraspinal
- ♥ Major muscle group with resulting compartment syndrome.

Life-threatening:

This is really a matter of extent, with uncontrolled *progression* of any of the above scenarios of moderate to severe bleeding, that results in worsening symptoms

Note that the above classification is a generalization only and other factors such as co-morbidities will also come into consideration in any particular individual patient.

Investigations

In the patient with significant bleeding:

1. FBE:
 - Hb / Platelets in particular.
2. Coagulation profile:

Parameter	Dabigatran effect (Thrombin inhibitor)	Factor Xa Inhibitors (Rivaroxaban/ Apixaban)
INR	Mildly prolonged	Variable
aPTT	Prolonged but with poor correlation with drug concentrations. aPTT > 90 seconds <i>suggests</i> a high drug level. Normal aPTT suggests minimal drug is present.	Variable
Thrombin Clotting Time (TT, TCT)	Very sensitive Normal values exclude the presence of drug. Exceeds measurement times of coagulometer at high concentrations.	Not useful
Haemoclot assay (dilute thrombin time)	Useful to derive levels	Not useful
Factor IIa (i.e. thrombin) assay	Best correlation with bleeding risk.	Not useful

Factor Xa assay	Not useful	Good correlation with levels.
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Notes:

- For dabigatran:
 - ♥ A combination of INR > 2 and aPTT > 90 seconds *suggests* high plasma levels of dabigatran.
 - ♥ Normal INR and normal aPTT *suggest* low plasma levels of dabigatran.
- For factor Xa inhibitors:
 - ♥ A combination of normal PT and aPTT *suggests* low plasma levels of apixaban and rivaroxaban.

Factor IIa, Xa and Haemoclot assays are only currently available in a few hospitals and can take more **than 24 hours to perform.**

Thromboelastography is effective at measuring anticoagulant activity of NOACs but specific assays have not yet been developed

4. U&Es/ glucose
5. Calcium level
6. Blood group and hold or Cross match as clinically indicated.

Management

Clinical experience in the setting of acute overdose as well as bleeding whilst on normal therapy is limited and so there should be close consultation with a Clinical Toxicologists and/ or Haematologist.

Acute deliberate overdose with apixaban:

1. Oral charcoal:
 - This may be given in cooperative patients and without airway concerns, within **4 hours** of ingestion.
2. Procoagulant blood products may be considered (see below)
3. Andexanet alfa:

- **This is an antidote under development, but is not yet currently available for clinical use.**

Note that hemodialysis is *not* useful for Apixaban (or rivaroxaban) overdose or toxicity (in contrast to dabigatran where it may be useful).

Significant bleeding whilst taking therapeutic apixaban:

As a *general* guide:

For Mild Bleeding:

- Stop apixaban therapy:

Anticoagulant should be ceased at least temporarily in all patients presenting with significant bleeding.

The timing of recommencement will be influenced by:

- ♥ The severity of the bleeding event
- ♥ The presence of ongoing risk factors for bleeding (e.g. anatomical lesions, persisting renal dysfunction).
- ♥ The initial indication for anticoagulant therapy.

- Hydration:

♥ Adequate hydration should be maintained to enhance renal clearance of apixaban

- Local compression measures where relevant
- Close observation/ monitoring

For Moderate to Severe Bleeding to Life Threatening Bleeding :

Above measures plus:

- Oral charcoal:

♥ May be given, if the last dose of apixaban was < 2 hours and there are no concerns about the airway.

- IV fluid resuscitation:

- ♥ Apart from volume resuscitation a good urine output is also useful as apixaban is partly renally excreted.
- RBCs as clinically required.
- Consider platelet transfusion:
 - ♥ If levels are less than $50 \times 10^9/L$ or the patient is on an anti-platelet agent.

Consider the use of one of the following haemostatic agents if bleeding continues and becomes life-threatening:

- **Prothrombinex-VF:** ³
 - ♥ This is possibly the best current option, till specific antidotes become available.
 - ♥ Give 50 U/kg IV, (or 8 x 500 unit vials for an average 80kg patient).
 - ♥ This may be repeated following consultation with Haematology

Or

- **FEIBA:**

FEIBA is an Anti-Inhibitor Coagulant Complex usually indicated for use in haemophilia A and B patients with inhibitors.

It contains Factors II, IX, and X, mainly non-activated, and Factor VII mainly in the activated form. The product contains approximately equal unitages of Factor VIII inhibitor bypassing activity and Prothrombin Complex Factors. In addition, 1- 6 units of Factor VIII coagulant antigen (FVIII C:Ag) per mL are present. ⁴

- ♥ Give 50 IU/kg

Or

- Anti-fibrinolytic agent:
 - ♥ IV bolus; Tranexamic acid 15-30mg/kg

Then consider:

- ♥ Continuous infusion Tranexamic acid at 1 mg/kg/hour.

Additionally correct the underlying cause of bleeding , where possible.

Note that there is *no* evidence that administration of coagulation factors in the *absence* of bleeding has any beneficial effect. Indeed the administration of coagulation factors in the *absence* of significant bleeding is associated with a risk of *thromboembolic* events.

Disposition:

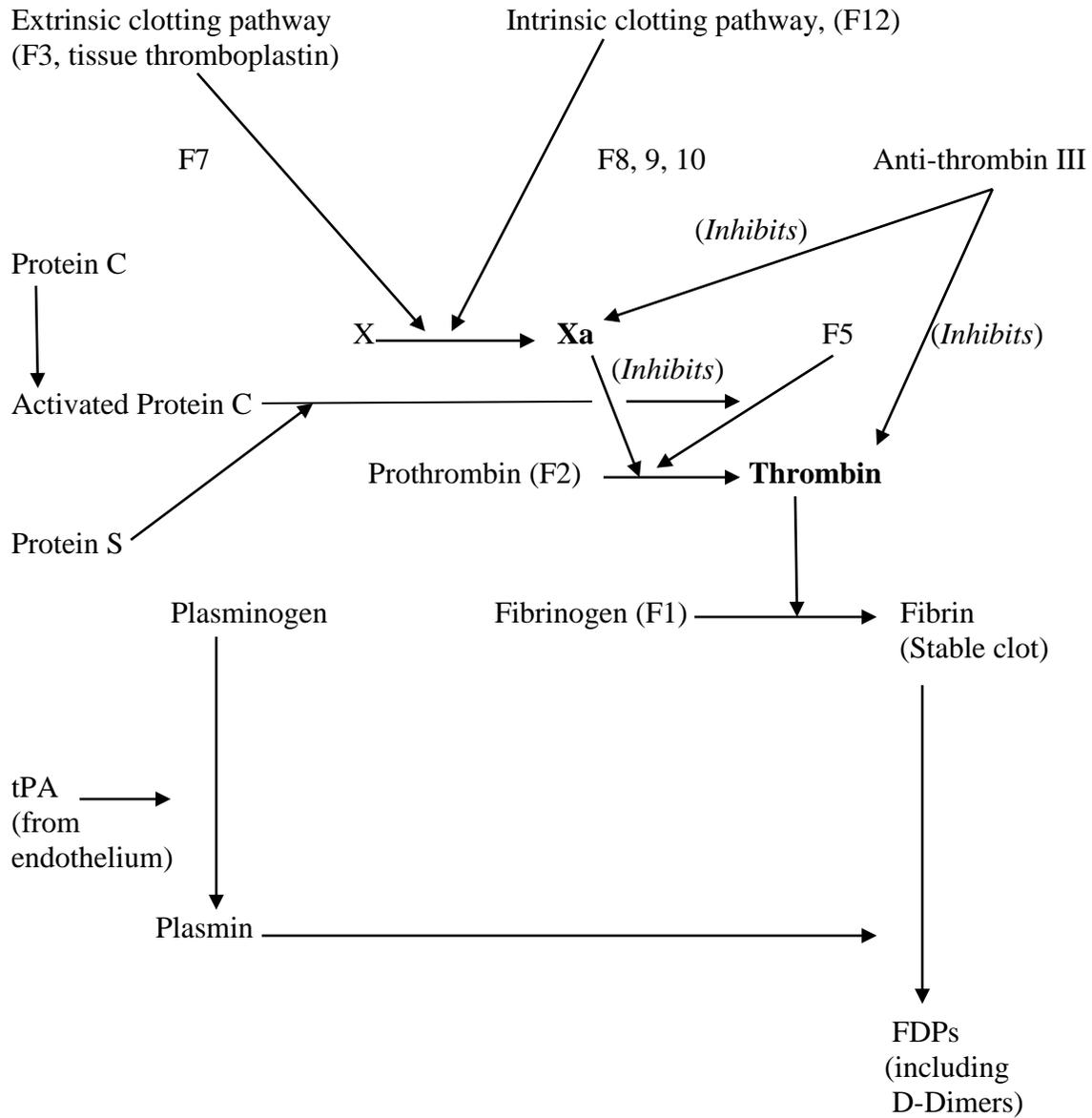
All patients who overdose on NOACs must be admitted to hospital for observation and serial coagulation studies until these are normalised.

All patients with NOAC related bleeding are admitted to hospital for active treatment as above.

Following factor Xa inhibitor overdose, patients are medically cleared if the PT and aPTT remain normal at 12 hours post ingestion.

Appendix 1

The coagulation cascade and fibrinolytic system:





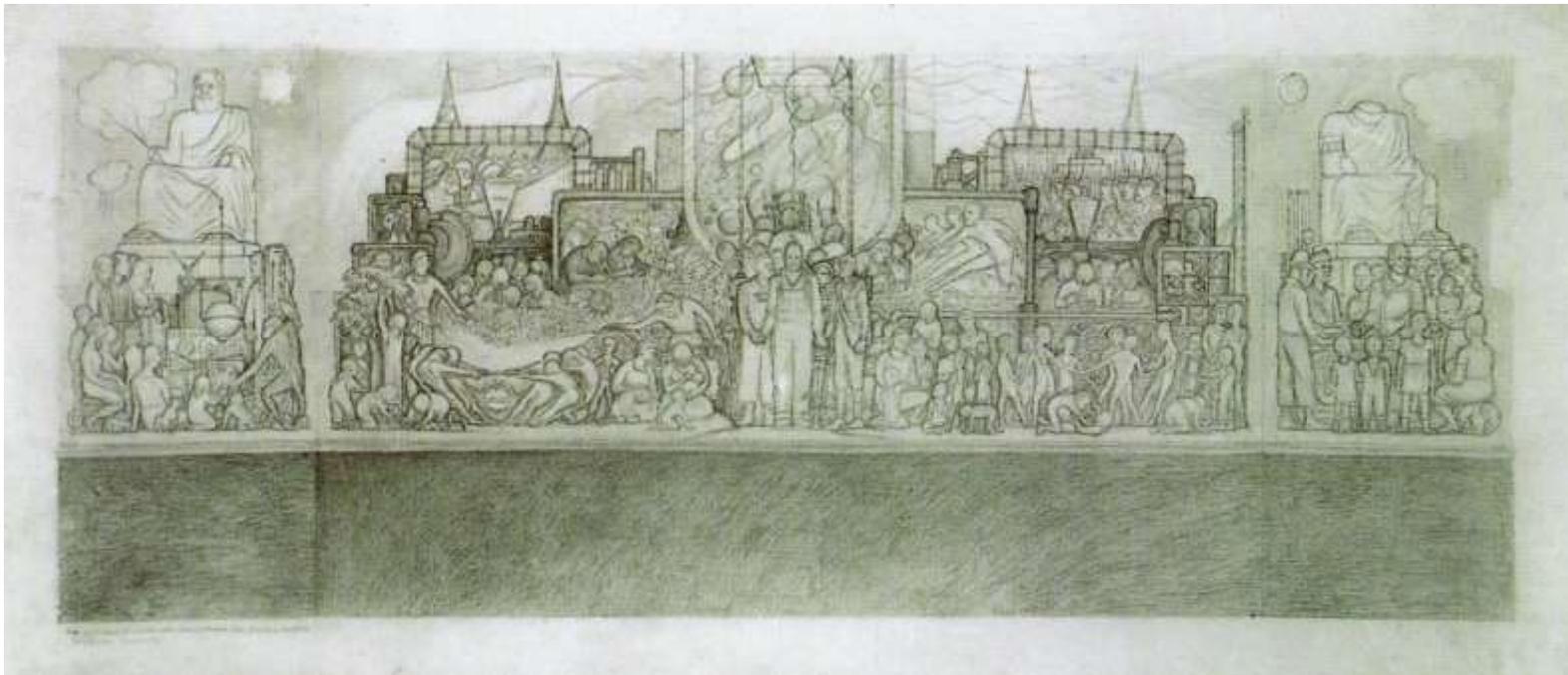
“Man Controller of the Universe”, Mural Fresco, 1934, (Detail) Diego Rivera, Palacio de Belles Artes, Mexico City - showing Lenin.



“Man Controller of the Universe”, Mural Fresco, 1934, (Detail) Diego Rivera, Palacio de Belles Artes, Mexico City - showing Trotsky, Engels and Marx.



*“Man
Controller of the
Universe”,
Mural Fresco,
1934, (Detail)
Diego Rivera,
Palacio de
Belles Artes,
Mexico City -
showing John
D. Rockefeller.*



Overall design for Diego Rivera's destroyed mural for the Rockefeller Center, “Man at the Crossroads, Looking with Hope and High Vision in the Choosing of a New and Better Future”, pencil on paper, 1932. Anonymous gift, Museum of Modern Art, New York City.

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3. Mike Makris, **Prothrombin Complex Concentrate (PCC)** for Non-Vitamin K Oral Anticoagulant (NOAC) reversal: Good enough for now? *Journal of Thrombosis and Haemostasis*. (Pending: doi: 10.1111/jth.12667)
4. New Oral Anticoagulants in L. Murray et al. *Toxicology Handbook* 3rd ed 2015.

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